Article

Retrospective study and review of ocular radiation side effects following external-beam Cobalt-60 radiation therapy in 37 dogs and 12 cats

Chantale L. Pinard, Anthony J. Mutsaers, Monique N. Mayer, J. Paul Woods

Abstract — This retrospective study evaluated the ocular side effects of cancer-bearing dogs and cats treated with external–beam Cobalt-60 (Co-60) radiation in which one or both orbit(s) were included in the radiation field. A total of 37 dogs and 12 cats presented to the Ontario Veterinary College during the 10-year study period (1999–2009) were evaluated. The radiation protocols ranged from a maximum of 60 Gray (Gy) in 24 fractions for curative intent to a minimum of 8 Gy in 1 fraction for palliative treatment. The main ocular side effect reported in both dogs and cats was conjunctivitis (79% and 55%, respectively). Other common ocular side effects included eyelid lesions in dogs (44%), ulcerative keratitis in cats (36%), and keratoconjunctivitis sicca in both dogs and cats (44% and 27%, respectively). The high incidence of ocular side effects in both patient populations indicates a need for regular ophthalmic examinations as a component of routine follow-up for radiation therapy involving the orbit. Radiation damage to ocular tissues is also reviewed.

Résumé — Étude rétrospective et examen des effets secondaires de la radiation oculaire après une radiothérapie externe au cobalt-60 chez 37 chiens et 12 chats. Cette étude rétrospective a évalué les effets secondaires oculaires chez des chiens et des chats atteints du cancer traités avec une radiation externe au cobalt-60 (Co-60) lorsque l'une ou l'autre des orbites étaient incluses dans le champ de radiation. Un total de 37 chiens et de 12 chats présentés à l'Ontario Veterinary College durant la période d'étude de 10 ans (1999–2009) ont été évalués. Les protocoles de radiation s'échelonnaient de 60 Gray (Gy) en 24 fractions pour un traitement curatif à un minimum de 8 Gy en 1 fraction pour un traitement palliatif. Le principal effet secondaire oculaire signalé chez les chiens et les chats était la conjonctivite (79 % et 55 %, respectivement). D'autres effets secondaires communs étaient des lésions des paupières chez les chiens (44 %), une kératite ulcérative chez les chats (36 %) et une kératoconjonctivite sèche chez les chiens et les chats (44 % et 27 %, respectivement). L'incidence élevée d'effets secondaires oculaires dans les deux populations de patients signale le besoin d'examens ophtalmologiques réguliers comme élément d'un suivi de routine pour la radiothérapie touchant l'orbite. Les dommages de la radiation aux tissus oculaires sont également examinés.

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Introduction

Radiation therapy is a common adjunctive therapy in the treatment of nasal, paranasal, and brain tumors in small animals (1–5). Megavoltage external beam radiation delivered by Cobalt-60 (Co-60) therapy machine or a linear accelerator is the most commonly used modality to treat tumors of the head region (6). Due to the proximity of the eyes to the nasal cavity and brain, ocular complications have been reported in humans (7), monkeys (8), mice (9,10), rats (10–12), rabbits (10), frogs (13), dogs (14–16), and cats (17). The ophthalmic complications include blepharitis, corneal ulceration and keratitis, keratoconjunctivitis sicca (KCS), cataracts, vascular retinopathy, and optic neuropathy (14–16).

Radiation therapy is delivered to small animal patients with a curative or palliative intent. The goal of curative (or definitive) intent therapy is to provide cure or long-term tumor control; therefore, protocols maximize chances of local tumor control while minimizing risk of significant late radiation side effects. Palliative therapy has the goal of providing relief of symptoms while resulting in little to no acute radiation side effects. However, ocular side effects, acute or late, can be seen

Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario (Pinard, Mutsaers, Woods); Department of Small Animal Clinical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan (Mayer).

Address all correspondence to Dr. Chantale L. Pinard; e-mail: cpinard@uoguelph.ca

with both curative and palliative protocols. Acute side effects, such as conjunctivitis, are usually first observed during radiation treatment, progress for the first 7 to 14 d after the end of radiation therapy, and may persist for 4 to 6 wk (6). These complications usually resolve spontaneously with symptomatic treatment. Late side effects, such as cataracts or retinal atrophy, occur months to years after the end of radiation therapy and may consist of non-reversible damage to the supporting stroma or vasculature of irradiated tissues leading to tissue fibrosis, necrosis, or infarction. Consequently, late side effects are more commonly seen with curative intent therapy as these patients live long enough to develop these side effects. The Veterinary Radiation Therapy Oncology Group (VRTOG) has established a radiation morbidity scoring scheme (0–3) to document acute and late side effects (18). Scoring of acute ocular side effects entails the following: grade 1 includes alopecia/epilation and mild conjunctivitis, grade 2 includes KCS, moderate to severe conjunctivitis, or iritis and non-ulcerative keratitis, and grade 3 includes severe keratitis with corneal ulceration, glaucoma and/or vision loss. Scoring of late ocular side effects entails the following: grade 1 includes alopecia, asymptomatic cataracts and KCS, grade 2 includes symptomatic cataracts, keratitis, corneal ulcers, minor retinopathy and mild to moderate glaucoma and grade 3 includes panophthalmitis, severe glaucoma, retinal detachment, and blindness.

Although studies exist on canine ocular side effects of radiation therapy, there is a paucity of studies on feline ocular side effects and side effects associated with palliative protocols. The objective of this study was to retrospectively evaluate, with the aid of the VRTOG grading scheme, acute and late ocular complications associated with curative and palliative radiation therapies in 37 dogs and 12 cats following Co-60 radiation with orbital fields.

Materials and methods

Canine and feline patients selected for this study had Co-60 radiation therapy (Theratron 780C; Theratronic International, 1987, Ottawa, Ontario) to 1 or both orbits while undergoing cancer treatment at the Ontario Veterinary College from 1999 to 2009. Thirty-seven dogs and 12 cats had either curative or palliative radiation therapies. Data collected included breed, age, sex, tumor type, and radiation protocol (number of fractions, total dose, radiation field location, shielding of eyes). Furthermore, data was collected on ocular anomalies noted prior to, during, and after radiation therapy.

Ocular examinations were done by a variety of clinicians (small animal interns, internal medicine residents, Diplomates of the American Veterinary College of Internal Medicine and Ophthalmology) and included direct ophthalmoscopy, Schirmer Tear Test, and fluorescein stain uptake. Indirect ophthalmoscopy and tonometry were inconsistently performed throughout the study period. An electroretinogram was used to assess retinal function in 1 canine case. Ocular side effects were characterized by adnexal disease (periocular alopecia and/or blepharitis), conjunctival disease (mild or severe conjunctivitis), tear production (< 15 mm/min), corneal disease (non-ulcerative and ulcerative keratitis), lenticular disease (cataract development), uveal disease (iritis), and retinal disease (retinal atrophy). Acute ocular side effects were defined as clinical signs detected during or within the first 3 mo after radiation treatment. Conversely, late ocular side effects were defined as clinical signs detected 3 or more mo following the last radiation treatment. The VRTOG grading (18) was applied to each case. In patients with 2 or more ocular side effects, each side effect was recorded as a separate clinical entity independently of unilateral or bilateral involvement; the tabulation of data was done on a per case basis.

The biologically effective dose (BED) was calculated for all radiation protocols for late effects ($\alpha\beta$ ratio assumed to be 3 Gy) and for acute effects ($\alpha\beta$ ratio assumed to be 10 Gy) using the formula:

$$BED = nd\,(1 + d/\alpha\beta)$$

where: n = number of fractions, d = dose per fraction, and $\alpha\beta$ = alpha-beta ratio. Survival rates were calculated using Kaplan-Meier and Log Rank analysis. Survival was measured from the first day of radiation treatment until death due to any cause. Animals were censored if they were lost to follow-up or were alive at the time of analysis. Statistical analysis was performed using MedCalc version 12.1.4 (MedCalc Software, Mariakerke, Belgium) and GraphPad Prism 4 (San Diego, California, USA).

Results

Canine patients

The most common canine breeds, in decreasing order, were golden retrievers (10), mixed breed (8), Labrador retrievers (4), German shepherds (2), Shetland sheepdogs (2), Doberman pinschers (2), and 1 each of the following: cardigan Welsh corgi, samoyed, border collie, vizsla, miniature dachshund, dalmation, English springer spaniel, chow chow, and basset hound. The sex distribution was 20 spayed females, 1 intact female, 12 castrated males, and 4 intact males. The age of the canine patients ranged from 4.5 to 14 y with a median of 8.75 y. At the end of the study, 26 canine patients were deceased, 7 were alive, and the status of 4 was unknown. Follow-up from the last radiation therapy ranged from 0 to 17 mo, with a median of 1.5 mo. The tumor type confirmed by biopsy (for 35/37 dogs), in decreasing order of frequency, was nasal adenocarcinoma (6), nasal chondrosarcoma (6), nasal carcinoma (6), oral melanoma (4), frontal sinus squamous cell carcinoma (2), and 1 each of the following: maxillary fibrosarcoma, maxillary fibroma, maxillary sarcoma, maxillary histiocytic sarcoma, nasal histiocytic sarcoma, nasal osteosarcoma, conjunctival melanoma, orbital fibrosarcoma, orbital soft tissue sarcoma, orbital lymphoma, and mandibular infiltrative lipoma. The remaining 2 cases had brain masses that were not biopsied.

Canine radiation protocols

The median radiation field size was 108 cm^2. The radiation field included 17 left eyes (with 8 cases having the right eye shielded), 10 right eyes (with 5 cases having the left eye shielded), and 10 bilateral cases (with 2 cases having the left and right eye shielded). The 6.0-cm lead shields were placed in a tray inserted into the collimator system over the patient, and were used to

Table 1. Ocular side effects tabulated per canine case

Ocular side effects	Curative (n = 20) Acute	Curative (n = 20) Late	Palliative (n = 14) Acute	Palliative (n = 14) Late	Total (%)[a]
Eyelid lesions	9	1[b]	5	0	15 (44)
Conjunctivitis	14[c]	2[b]	11	0	27 (79)
KCS	8	2	4[d]	1	15 (44)
Keratitis	6	4	4	0	14 (41)
Ulcerative keratitis	5	1	3	0	9 (26)
Cataract	0	3	0	2	5 (15)
Uveitis	0	0	0	0	0 (0)
Retinal lesions	0	1[e]	0	0	1 (3)

KCS — keratoconjunctivitis sicca.
[a] (%) percentage of total cases.
[b] Associated with late KCS.
[c] 1 case reported in shielded eye and 2 cases were deemed severe.
[d] 1 case reported in shielded eye.
[e] Retinal atrophy confirmed by electroretinography.

Table 2. Ocular side effects tabulated per feline case

Ocular side effects Clinical signs	Curative (n = 5) Acute	Curative (n = 5) Late	Palliative (n = 6) Acute	Palliative (n = 6) Late	Total (%)[c]
Eyelid lesions	3	0	2	0	5 (45)
Conjunctivitis	3	0	3	0	6 (55)
KCS	2[a]	0	1	0	3 (27)
Keratitis	2[a]	0	1[b]	0	3 (27)
Ulcerative keratitis	3[a]	0	1[b]	0	4 (36)
Cataracts	0	0	0	1	1 (9)
Uveitis	1	0	0	0	1 (9)
Retinal lesions	0	0	0	0	0 (0)

KCS — keratoconjunctivitis sicca.
[a] Denotes same case with history of FHV.
[b] Denotes same case with history of FHV.
[c] (%) percentage of total cases.

spare the contralateral eye. No additional beam modifying devices or bolus materials were used. Twenty-two patients received a curative intent protocol and 15 received a palliative protocol; only 1 canine patient, receiving curative intent protocol, did not complete the intended protocol (missed 1 fraction). In most cases, the curative protocols were delivered on a daily basis Monday to Friday and the palliative protocols were delivered on a weekly basis. The curative radiation protocol included 60 Gy in 24 fractions (3), 54 Gy in 18–21 fractions (2), 50 Gy in 18–20 fractions (14), and 45 Gy in 15–20 fractions (3). The palliative protocols included 36 Gy in 6 fractions (2), 36 Gy in 4 fractions (2), 32 Gy in 4 fractions (7), 24 Gy in 3 fractions (3), and 18 Gy in 3 fractions (1). Two curative intent and 2 palliative intent cases received additional radiation (curative: single dose of 10 Gy each; palliative: 8 Gy given as a single dose and 16 Gy given as 2 doses of 8 Gy). The additional boost treatments given with the curative intent were done at the end of the therapy protocol; the palliative additional treatments were given 5 and 7 mo after the last treatment, respectively, in order to alleviate recurring clinical signs.

Feline patients

The most common feline breed was American domestic (9), with the remaining being 1 each of Maine coon, ragdoll, and Burmese. The gender distribution was 8 castrated males and 4 spayed females. The age for the feline patients ranged from 4 to 17.5 y with a median of 9 y. At the end of the study, 5 cats were deceased and the remainder were lost to follow-up. Follow-up from the last radiation treatment ranged from 0 to 36 mo, with a median of 2.75 mo. One case had no follow-up recorded following the radiation therapy. The tumor type confirmed by histopathological biopsy (10) or fine-needle aspirate (2), in decreasing order of frequency, was nasal lymphoma (3), nasal adenocarcinoma (3), nasal carcinoma (2), brain melanoma (1), maxillary chondrosarcoma (1), facial plasmacytoma (1), and oral lymphoma (1).

Feline radiation protocols

The median field size of radiation was 64 cm^2. The radiation field included 5 right eyes (with 4 cases having the left eye shielded), 4 left eyes (with 2 cases having the right eye shielded), and 3 cases with bilateral involvement. The curative protocols included 50 Gy in 20 fractions (4) and 47.5 Gy in 19 fractions (1). The palliative protocols included 32 Gy in 4 fractions with 2 extra fractions (8 Gy each) given as additional treatment 5 months post last treatment (1), 40 Gy in 10 fractions (1), 36 Gy in 6 fractions (1), 32 Gy in 4 fractions (2), and 8 Gy in 1 fraction (2).

Canine and feline ocular complications

Ocular examination findings existed for 34 canine cases (2 curative cases had enucleation prior to radiation therapy; 1 palliative case was lost to follow-up after last radiation treatment) (Table 1) and 11 feline cases (1 palliative case was lost to follow-up after last radiation therapy) (Table 2). Very few of the patients (5 dogs and 3 cats) received an ocular examination prior to the start of the radiation protocol. Data from the ocular examinations was recorded once a presenting ocular lesion was noted by the owner or clinician; follow-up examinations were done at the discretion of the clinician and owner. All but 4 canine cases (88%) and all but 2 feline cases (82%) had ocular anomalies noted following either curative or palliative radiation therapy. Half the canine patients and 55% of the feline patients had 3 or more ocular clinical signs. The canine and feline cases reported a median of almost 2.5 and 2 clinical signs per case, respectively. Acute and late ocular side effects were seen in both patient populations with both types of protocols. Ocular side effects included periocular alopecia with accompanying blepharitis, conjunctivitis, KCS, keratitis, ulcerative keratitis, cataract, uveitis, and retinopathy. Overall, the most common canine ocular complication was conjunctivitis (79%) and the least common was retinopathy (3%). In cats, conjunctivitis was also the most common presenting complaint (55%) with no retinopathy being recorded. Uveitis was not detected in the canine population but was noted in 1 feline case. Cataracts were noted as a late side effect in canine (8 to 11 mo) and feline (6 mo) patients. The single case reporting retinopathy was diagnosed as retinal atrophy due to poor retinal function detected by an electroretinogram in 1 dog (chow chow). Anecdotally, reports of night and day blindness from owners was reported but never

Table 3. VRTOG acute radiation scores of canine curative and palliative cases

Grade	Curative	Palliative
1[a]	21 (62%)[d]	16 (47%)
2[b]	16 (47%)	8 (24%)
3[c]	6 (18%)	3 (9%)

[a] Grade 1 includes alopecia/epilation and mild conjunctivitis.
[b] Grade 2 includes KCS, moderate to severe conjunctivitis or iritis and non-ulcerative keratitis.
[c] Grade 3 includes severe keratitis with corneal ulceration, glaucoma and/or vision loss.
[d] Percentage of total number of cases (n = 34).

Table 4. VRTOG acute radiation scores of feline curative and palliative cases

Grade	Curative	Palliative
1[a]	6 (55%)[d]	5 (45%)
2[b]	4 (36%)	2 (18%)
3[c]	4 (36%)	1 (9%)

[a] Grade 1 includes alopecia/epilation and mild conjunctivitis.
[b] Grade 2 includes KCS, moderate to severe conjunctivitis or iritis and non-ulcerative keratitis.
[c] Grade 3 includes severe keratitis with corneal ulceration, glaucoma and/or vision loss.
[d] Percentage of total number of cases (n = 11).

confirmed in 2 canine patients having received a curative protocol and 1 canine patient having received a palliative protocol. Sporadic ocular side effects (conjunctivitis, corneal ulcer, KCS, and keratitis) were detected in 5 canine shielded eyes in 3 curative and 2 palliative intent protocols.

As expected, curative protocols had more patients with clinical signs than palliative protocols in both populations. Common acute effects noted in curative protocols included adnexal anomalies and KCS, whereas keratitis was more prevalent as a late effect. Although some of the clinical signs, such as KCS and keratitis, were shared between acute and late onset appearance, conjunctivitis was the most common acute side effect and cataract was the most frequent late onset side effect in canine populations, independent of the protocol. In cats, no difference was seen between acute side effects with both curative and palliative protocols but acute effects were detected at a higher frequency than were late onset effects. Two feline patients suffered from feline herpes virus type I infection and had a variety of clinical signs associated with this infection (Table 2).

The VRTOG scores for acute and late ocular side effects are shown in Tables 3 to 5. The majority of the cases in both populations of patients had Grade 1 lesions. The only exception is the higher percentage of grade 2 late-occurring lesions in the canine cases receiving palliative protocols. This anomaly was due to the development of cataracts in 2 cases in a small sample population that lived long enough to have late effects of radiation. The feline patients had only 1 late effect lesion (cataract development in a palliative protocol).

Standard treatments for ocular disease encountered were instituted as ocular side effects were observed. Response to treatment was noted in all cases entailing adnexal disease, ocular discharge, conjunctival and corneal disease, as well as KCS. These treatments included the topical application of an antibiotic (bacitracin-neomycin-polymixin B; fusidic acid, tobramycin), antibiotic-steroid combination (bacitracin-neomycin-polymixin B-hydrocortisone; neomycin-polymixin B-dexamethasone), non-steroidal anti-inflammatory drug (diclofenac), tear stimulant (0.2% cyclosporine; tacrolimus), and artificial tear/gel. Systemic medication used to treat some of the ocular diseases included meloxicam, prednisone, doxycycline, and cephalexin.

For canine curative intent protocols, the median BED_{3Gy} was 91.7 (range: 78 to 110), and the median BED_{10Gy} was 62.5 (range: 50.7 to 75). For canine palliative intent protocols, the median BED_{3Gy} was 117.3 (range: 88 to 144), and the median BED_{10Gy} was 57.6 (range: 43.2 to 68.4).

For feline curative intent protocols, the median BED_{3Gy} was 91.7 (range: 87.1 to 91.7), and the median BED_{10Gy} was 62.5 (range: 59.4 to 62.5). For feline palliative intent protocols, the median BED_{3Gy} was 108 (range: 29.3 to 117.3), and the median BED_{10Gy} was 57.6 (range: 14.4 to 57.6).

Median survival times were the following: 210 d for canine curative protocols (22 dogs); 298 d for canine palliative protocols (15 dogs); 119 d for feline curative protocols (5 cats) and 280 d for feline palliative protocols (7 cats). This survival difference was not significant for canine patients (P = 0.98) but it was significant for feline patients (P = 0.02). Remarkably, 1 cat receiving palliative protocol was alive 3 y after treatment.

Discussion

Ocular side effects occur if the orbits are within the radiation field and all ocular tissues can be affected by radiation (4,14–16). Although previous studies included different radiation protocols, the present study reports similar ocular side effects following megavoltage radiation of the orbital region. Adams et al (4) reported that dogs receiving between 40 to 42 Gy in 9–10 fractions of Co-60 radiation had acute (mild conjunctivitis, blepharitis, keratoconjunctivitis) and late (retinopathy, cataracts, KCS, anterior uveitis, corneal ulcer) side effects. Another study reported dogs receiving 36 to 67.5 Gy in 8–42 fractions of Co-60 radiation had ocular complications which included acute (mild conjunctivitis, KCS, keratoconjunctivitis, ulcerative keratoconjunctivitis) and late (posterior segment changes, cataracts, anterior uveal changes) side effects (14). A third study reported dogs receiving 36 to 50 Gy (9–12 fractions) radiation by a linear accelerator had ocular complications that included acute (severe keratitis, conjunctivitis, KCS, uveitis) and late (cataract, severe keratitis, KCS) side effects (16). The acute effects in the current study, in decreasing frequency, included conjunctivitis, blepharitis, KCS, keratitis, and ulcerative keratitis with both curative and palliative protocols in both species. Late side effects included keratitis, cataracts, KCS, ulcerative keratitis and retinal atrophy and these were mostly seen in canine curative protocols. Cataracts were the only late effect detected in the feline palliative protocol. As seen with previous studies (4,14,16), our study showed that late side effects were more vision threatening and more prevalent in curative protocols. This finding is anticipated as patients receiving curative protocols usually live longer than those patients receiving palliative protocols. The low number of cases could also explain why no difference was seen in acute side effects

Table 5. VRTOG late radiation scores of canine curative and palliative cases

Grade	Curative	Palliative
1[a]	6 (18%)[d]	1 (3%)
2[b]	6 (18%)	2 (6%)
3[c]	2 (6%)	0 (0%)

[a] Grade 1 includes alopecia, asymptomatic cataracts and KCS.
[b] Grade 2 includes symptomatic cataracts, keratitis, corneal ulcers, minor retinopathy and mild to moderate glaucoma.
[c] Grade 3 includes panophthalmitis, severe glaucoma, retinal detachment, and blindness.
[d] Percentage over total number of cases (n = 34).

with curative and palliative protocols. Although acute effects were detected at a higher frequency than late onset effects in our feline population, this fact may be heavily influenced by the short survival times in this feline population.

Of note, 2 feline patients suffering from feline herpes virus type I infection had a variety of clinical signs that could be associated with this infection. Although it is possible that the scored toxicity was solely due to viral infection rather than radiation, it is plausible and more likely that the radiation therapy (along with the hospital visit, including general anesthesia) was responsible for re-activation of the herpetic infection. Lastly, this study appeared to demonstrate a significant difference in survival time for feline patients receiving palliative versus curative intent protocols; however, the number of cats in each group was small, and this result may be influenced by prognostic factors such as tumor type, grade, and distribution of disease stage within each group, which were not evaluated in this study.

Our study differs from previous studies reporting canine ocular lesions due to the inclusion of patients receiving less than 36 Gy. There is a paucity of data on ocular side effects from patients receiving palliative protocols. In our study, canine and feline patients receiving palliative protocols did develop acute side effects with a few being vision threatening (Grade 3 VRTOG). Although palliative protocols have higher radiation doses per treatment compared with curative protocols, the number of treatments is less and therefore the occurrence of acute side effects is generally not expected. The development of acute side effects in our palliative protocols could be due to the total dose and fraction size as indicated by the relatively high BED_{10Gy}. In addition, our study reported ocular side effects of radiation in feline patients. Our study demonstrated similar ocular side effects in feline patients compared with canine patients with both curative and palliative protocols.

Previous studies described the degree of change and destruction that occurs in canine eyes following radiation therapy (14,15). Radiation-induced inflammation negatively influences the cell's ability to regenerate and may be due to the disruption of mitotic activity (19). Late radiation side effects damage the tissues and supporting vasculature, leading to tissue fibrosis and/or necrosis (6). Once damage has occurred, it is unlikely that injured tissues will recover (15).

Radiation therapy induced KCS occurs due to damage to meibomian glands (20) and lacrimal glands (21,22). This acute side effect has been noted in humans following doses of 24 to 25.5 Gy (23). Dysfunction of these glands leads to tear oil and aqueous deficiency and subsequent corneal dessication with possible ulceration. The probability of recovery of function of these glands is diminished with increased radiation doses (7). The possibility of atrophy and fibrosis of human lacrimal glands increases dramatically with doses $\geq$ 50 Gy (7) and permanent loss of secretion of tears and absolute KCS is seen with doses $>$ 60 Gy (19). "Tolerance" doses for the human lacrimal gland are between 30 to 40 Gy (24,25). In order to minimize eyelid and lacrimal side effects, it is therefore recommended to use smaller fractions with longer treatment protocols (26). Artificial tears may help compensate for the loss of meibomian gland function. An alternative is autologous serum as its biochemical properties resemble those of natural tears (25). Topical application of 0.2% cyclosporine and/or 0.02% to 0.03% tacrolimus are also recommended in cases of confirmed canine KCS (27,28). No effective treatment for feline KCS has been developed.

Conjunctivitis is a common acute side effect seen with radiation therapy (14–16). In dogs, conjunctivitis can occur within 1 mo of radiation therapy and continue as a chronic side effect for 2 y (15). Acute conjunctivitis is reported in humans with doses $\geq$ 30 Gy (29). Chronic conjunctivitis has been reported in humans with $>$ 50 Gy (30). Symblepharon has been reported in humans with doses $>$ 60 Gy (31). In humans, it is recommended that preservative-free artificial tears be used 4 to 8 times daily to relieve the irritation caused by conjunctivitis (7). Topical antibiotics and antivirals should only be used if there is strong evidence of infection. Amniotic membrane transplantation can be used to reconstruct conjunctival defects associated with a symblepharon (32).

Keratitis and ulcerative keratitis were detected in our study. Canine corneal basal stem cell layer may be vulnerable to direct radiation effects which lead to ulcerative keratitis with consequently protracted healing times (15,19). In addition, the radiation damage to canine lacrimal and meibomian glands (14,15) and the resulting KCS further impede corneal healing in irradiated patients. Corneal atrophy, thinning of the corneal epithelial layer, and keratitis were noted in 1 canine study within 1 mo of radiation and persisted as long as 2 y (15). In humans, punctuate corneal erosions are common with fractionated radiation therapy doses of 30 to 50 Gy (33). Corneal edema due to loss of epithelial cells or endothelial function has been reported in humans with doses of 40 to 50 Gy (33). Corneal ulceration due to loss of epithelium and stroma has been reported in humans receiving fractionated radiation doses $>$ 60 Gy but also with 20 Gy delivered in a single dose (33). In order to reduce corneal toxicity it is recommended that the radiation delivery be carefully planned in order to minimize side effects. This can be accomplished with eye shields (34). With veterinary patients, continuous wearing of Elizabethan collars will help diminish self trauma to the cornea, especially in the face of periocular and adnexal lesions. Epithelial erosions should be treated with topical lubricants and corneal edema can be resolved with hypertonic saline ointments. Topical corticosteroids can be used but care must be taken to avoid long-term therapy as breakdown of the cornea's extracellular matrix may occur. Glued-on rigid gas-permeable contact lenses have been used with success in humans with severe radiation-induced keratitis (35).

Acute early iritis has been reported in humans after single doses of ≥ 10 Gy (7). Although in this study uveitis was only seen in 1 feline patient as an acute side effect in a curative protocol, anterior uveal changes have been reported as an acute (15) and late radiation effect caused by vascular damage (15,19). This damage leads to tissue ischemia, necrosis, and secondary connective tissue proliferation (19). Histological analysis of irradiated uveal tissues does not corroborate features of inflammation but points to a breakdown of the blood ocular barrier from vascular damage (14). The resulting neovascularization of the iris and iridocorneal angle following radiation therapy can lead to neovascular glaucoma. Although this type of glaucoma has been reported in up to 20% of irradiated eyes as a late complication in humans (7), there are no such reports in the veterinary literature. In humans, additional risk factors include higher radiation therapy doses, diabetes mellitus, vitreous hemorrhage, and retinal detachment (36). In addition to limiting the radiation of the anterior chamber, careful monitoring of diabetic patients is recommended. In humans, laser panretinal photocoagulation or peripheral cryotherapy has been effective in inducing regression of iris neovascularization and preventing progression of glaucoma if performed early in the course of the disease. Intravitreal administration of an anti-vascular endothelial growth factor (VEGF) agent such as bevacizumab has shown promising results as an adjunctive therapy to the laser panretinal photocoagulation or to standard retinal ablative procedure (37).

Radiation damage to the anterior cuboidal lens epithelium and alteration with normal differentiation and appropriate lens fiber deposition lead to cataract formation. Deficits or modifications in the metabolism of cortical lens fibers may also be involved in the formation of cataracts in irradiated patients (38,39). Due to the slow lens epithelium turnover rate, radiation side effects may not be clinically detected for 3 to 6 mo, as seen with our study. Ching et al (15) reported equatorial to subcapsular and cortical cataracts developing in dogs as early as 3 mo but with the greatest frequency between 6 mo to 1 y. In rats, male gender is a risk factor (40) and cataracts can develop after a single fraction dose as low as 2 Gy (7). The time of onset for human cataracts following radiation therapy is dose related; an increased possibility of cataract is linked with increasing fraction size and shorter treatment time (41). In humans, customized lens shields with lens-sparing radiation techniques (42) can reduce the risk of cataract formation. Furthermore, heparin may have a protective effect (43). However, if cataracts impair vision, cataract surgery is indicated if retinal function is adequate.

In our study, 1 canine patient was diagnosed with retinal atrophy by an electroretinogram as cataracts prevented direct evaluation of the fundus. Intraretinal and subretinal haemorrhages have been reported in dogs (14,15). Radiation-induced retinopathy is due to retinal blood vessel damage and does not appear to be impacted by the total radiation dose received but by the daily dose (19). Degeneration of the outer retinal layers (loss of photoreceptors' outer segments) has been documented as early as 1 mo in dogs (15). Additional retinal lesions such as retinal hemorrhage and degenerative vasculopathy occurred at 3 to 6 mo (15). Loss of ganglion cells, sclerotic retinal blood vessels and optic nerve axonal degeneration were detected 1 to 2 y after radiation therapy in dogs (15). In humans, retinopathy commonly appears 6 mo to 3 y following radiation therapy (44). The latent period is shorter with doses of 70 to 80 Gy with 85% of human eyes showing retinal lesions within 3 mo (7). In humans, the threshold dose for retinal damage is thought to be 30 to 35 Gy (7). There are no proven treatments for radiation retinopathy. It is recommended that fully fractionated therapy be delivered to the lowest effective dose. Stable or improved visual acuity has been shown in 86% of human patients receiving intravitreal bevacizumab (45).

This retrospective study relied on data collected by several clinicians over a 10-year period. Previous studies have used a standard ophthalmic examination for the duration of the study (14–16) and consistently had pre-radiation ocular examinations as well as set time points for follow-up examinations. This study had inconsistent pre-radiation ocular examinations and only had data on ocular side effects that arose during the follow-up. As several clinicians were involved, the description of ocular side effects was subjective and differences may have occurred in the assessment of severity of lesions. Furthermore, as no consistent time points for examinations were followed, ocular side effects and their greatest severity could have been missed. Lack of sufficient follow-up times to detect late effects in curative protocols is another limitation of this study. As with previous studies (4,14–16) the dose to the various ocular structures was not calculated and therefore this study cannot properly assess the incidence of effects related to dose. Although the number of canine cases was similar to those of previous studies, the number of feline cases was low. However, due to the paucity of information on feline ocular side effects following radiation therapy, the authors elected to report their findings on this species.

In conclusion, conventional megavoltage radiation therapy involving orbital regions induce ocular side effects that are more frequent, severe and vision threatening with curative protocols than with palliative protocols in both dogs and cats. Acute effects occur at a higher frequency than late effects in curative protocols in both populations of patients. Late side effects may not be as prevalent in palliative patients due to the patient's shortened lifespan. Benefits of therapy and risks of acute and late ocular complications should be discussed with owners prior to treatment as they may have an important impact on the patient's quality of life. Although some ocular side effects can be managed with topical therapy (e.g., conjunctivitis), others can progress and become nonreversible requiring either surgical repair or enucleation if serious complications arise (e.g., chronic KCS). Resolution of acute effects can be seen within a few months of radiation therapy; however, late effects can require lifelong therapy and constant monitoring. Regular follow-up ocular examinations with possible referral to a veterinary ophthalmologist are required with these patients in order to have prompt and appropriate management of these side effects and potentially avoid serious complications. CVJ

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